Imaging of the left atrium: useful to predict stroke?

Electrophysiological imaging of the LA

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Disclosures

Consultant: Biosense-Webster, Biotronik, St. Jude

Research Grants and Speaker Board: Biosense-Webster, St. Jude, Bard EP, Biotronik

Thromboembolism in AF (AFFIRM database)

- Not all strokes in AF are cardioembolic
- Mostly due to lack of or subtherapeutic anticoagulation
- Current assessment of the absence of all AF unsatisfactory – asymptomatic AF

	N= 4060
All strokes	211(8.2%)
Ischemic strokes	157(6.3%)
1° Intra-cerebral h'hage	34(1.2%)
Subdural/arachnoid h'hage	24(0.8%)
Ischemic stroke mechanism	
Cardioembolic	35/71(49.3%)
Atheroembolic	12/71(16.9%)
Lacunar	19/71(26.8%)
Unknown	86 (54.8%)
Probably cardioembolic	50/83(60.2%)

Cardioembolic + probably cardioembolic stroke = 55%

Sherman et al, Arch Intern Med. 2005;165:1185-1191

Cardioembolic vs. Noncardioembolic Strokes in Atrial Fibrillation

- 3,950 participants in the Stroke Prevention in Atrial Fibrillation I–III clinical trials
- Strokes were classified by presumed mechanism
- 217 ischemic strokes:
  - 52% classified as probably cardioembolic
  - 24% noncardioembolic, and
  - 24% of uncertain cause (i.e., 68% of classifiable infarcts were deemed cardioembolic)
- 56% ischemic strokes in AF patients taking warfarin were noncardioembolic vs. 16% of in those taking aspirin.

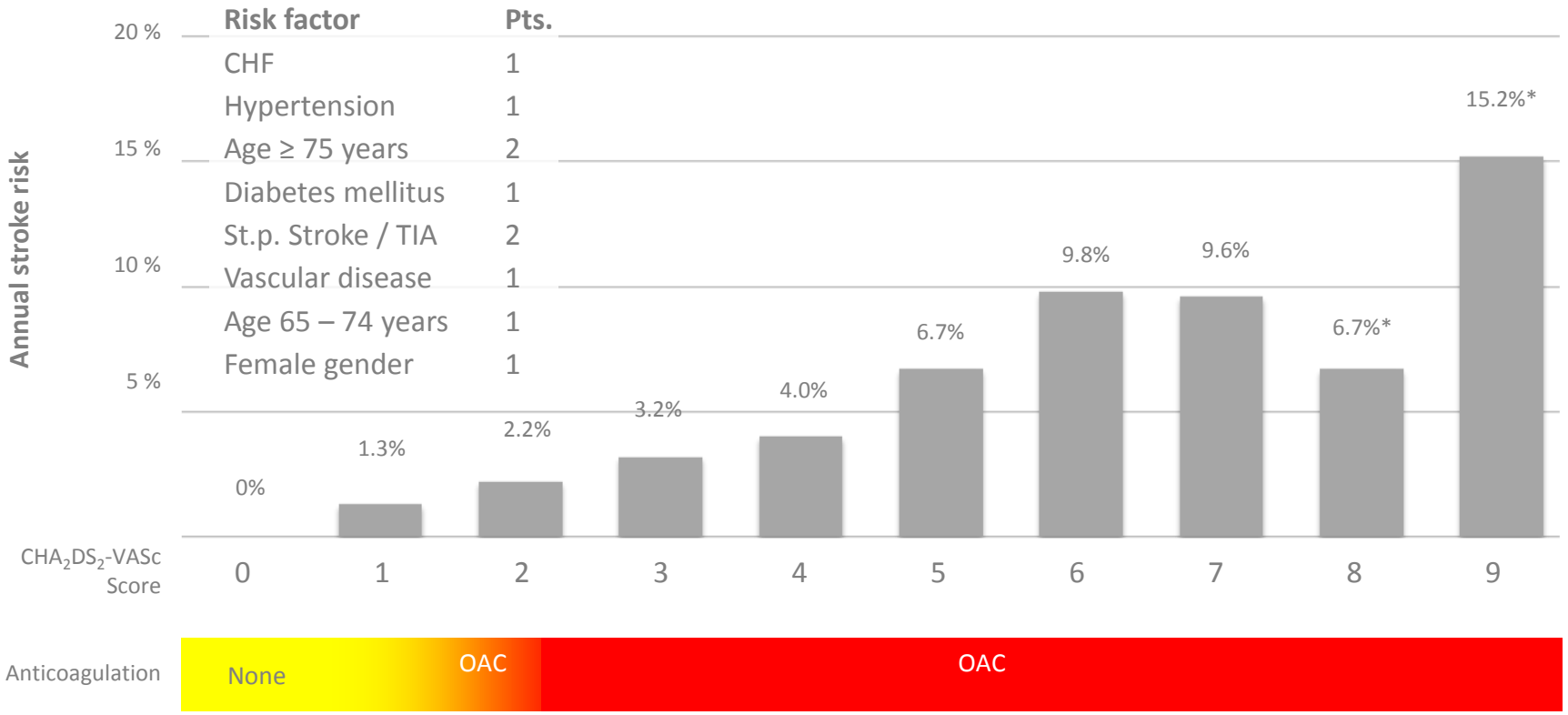
Hart R.G et al, Cerebrovasc Dis 2000;10:39–43

Is atrial fibrillation always a culprit of stroke in patients with atrial fibrillation plus stroke?

- Consecutive patients with ischemic stroke within 7 days of symptom onset and with AF
- Of 522 patients, 424 (81.2%) were grouped as AF-related stroke and the remaining 90 (17.2%) were classified as AF-unrelated stroke
- Of AF-unrelated stroke, 51 (9.8%) were categorized as possible large artery atherosclerosis and 38 (7.3%) as possible small artery occlusion
- AF is not always a culprit of stroke in patients with AF plus ischemic stroke; approximately one sixth are unrelated to AF and have distinct characteristics compared to AF-related stroke.

Kim SJ et al, Cerebrovasc Dis. 2013;36(5-6):373-82

Assessment of major and relevant risk factors



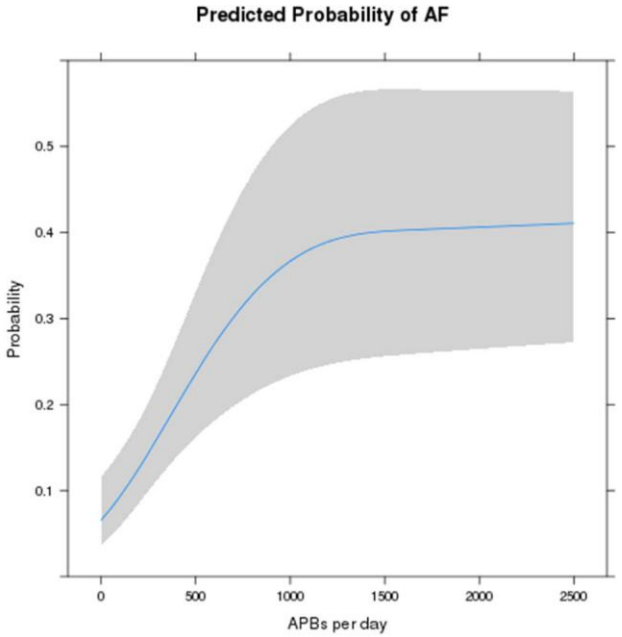
*ASA + Clopidogrel only, if patient does not tolerate or wish OAC (NOAC / VKA) – not because of bleeding issues[1]

1. Adapted from Camm AJ et al. Eur Heart J. 2012 Nov;33(21):2719-47.

Predictors of Ischemic Stroke

- **Well accepted: CHA2DS2VASC score**
- **Others**
  - High rate episodes
  - Duration, atrial fibrillation category
  - LA size: diameter, planimetered area, volume
  - LA contractility, LAA emptying velocity, SEC in LA
  - LA scars
  - Signal averaged P wave duration
  - Interatrial block

Stroke and Atrial ectopics, LA volume, P wave duration etc..



- Cryptogenic stroke or TIA w/o known AF
- 30-day ECG monitoring with an AF auto-detect external loop recorder
- Holter APB count/24 h

Table Characteristics of all cases and of those with and without AF identified

	All	No AF	AF	*p* Value
Age, y	51.5 (13.9)	48.9 (13.9)	59.2 (11.0)	0.018
Male, n (%)	28 (54.9)	22 (57.9)	6 (46.2)	0.5
Interval to insertion, d	174 (134)	181 (148)	151 (74)	0.5
CHADS2	2 (2-3)	2 (2-3)	3 (2-3.5)	0.003
CHA2DS2-VASc	3 (2-4)	3 (2-3)	4 (3.5-4)	0.001
Pre-ILR monitoring, d	1 (1-2)	1 (1-2)	1 (1-1.5)	0.9
APC per day	5 (1-23)	5 (1-13)	44 (5-765)	0.004
LA volume indexed, mL/m^2	25.6 (9.57)	23.1 (9.6)	30.6 (10.0)	0.025
Max P-wave duration, ms	121 (14.6)	120.5 (15.3)	125.8 (8.6)	0.3
Interatrial block, n (%)	25 (49)	16 (48.5)	9 (90.0)	0.02
PFO[b]	22/30	18/25	4/5	0.71

- Cohort study of 51 cryptogenic stroke patients with IL
- AF identified in 25.5%

Cotter et al, Neurology" 2013;80:1546–1550

***Gladstone D et al, Stroke*. 2015;46:936-941**

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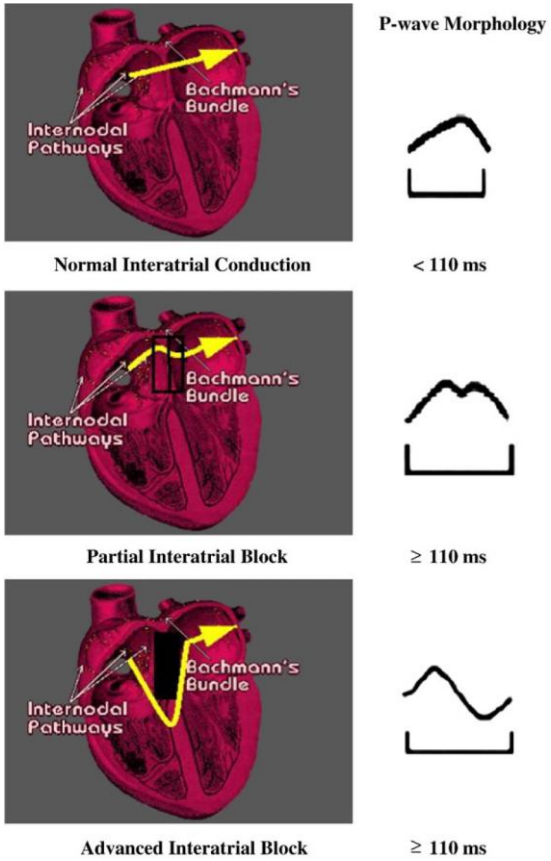
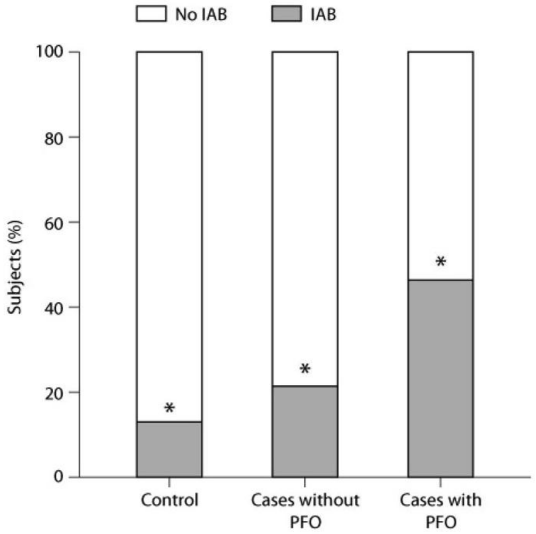
Abnormal atrial activation

- **Normal P-wave duration: less than 110 milliseconds**
  - normal transit time throughout the right and left atrium (RA and LA)
- **Interatrial block: prolonged conduction time between RA and LA resulting in prolonged P-wave duration ≥110 ms.**
- **IAB has associations LA enlargement, AF, other SVTs, systemic emboli, and myocardial ischemia**
- **Associated with PFO and stroke**





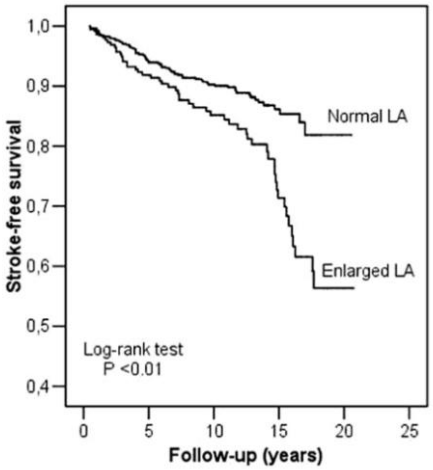
Cotter et al,
Cerebrovasc Dis Extra 2011;1:36–43

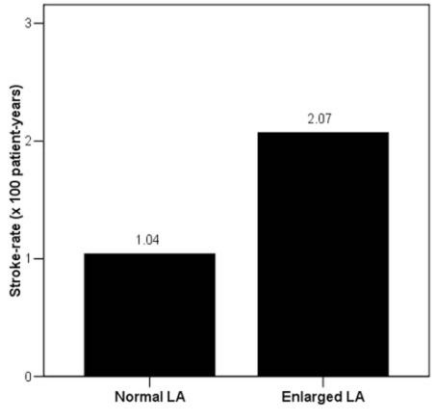
Kitkungvan et al, Journal of Electrocardiology 42 (2009) 687–692

Left atrial enlargement and stroke in hypertension

Table 2. Results of univariable analysis

Parameter	HR (95% CI)	*P* value
Age, 1 year	1.11 (1.09–1.14)	<0.01
Clinic SBP, 1 mm Hg	1.01 (1.00–1.02)	<0.01
Daytime SBP, 1 mm Hg	1.02 (1.01–1.04)	<0.01
Nighttime SBP, 1 mm Hg	1.03 (1.02–1.04)	<0.01
24-h SBP, 1 mm Hg	1.03 (1.02–1.04)	<0.01
Diabetes, yes vs. no	1.79 (1.09–2.94)	0.02
LV hypertrophy, yes vs. no	1.68 (1.19–2.35)	<0.01
Circadian BP changes group		
Dippers with MS <23 mm Hg	1.00 (referent)	
Dippers with MS >23 mm Hg	2.49 (1.44–4.31)	<0.01
Nondippers	2.10 (1.35–3.27)	<0.01
LA enlargement, yes vs. no	1.93 (1.36–2.72)	<0.01
New onset AF, yes vs. no	1.67 (0.99–2.82)	0.06
Previous events[a], yes vs. no	1.56 (0.84–2.91)	0.10
Sex, men vs. women	0.80 (0.57–1.13)	0.20

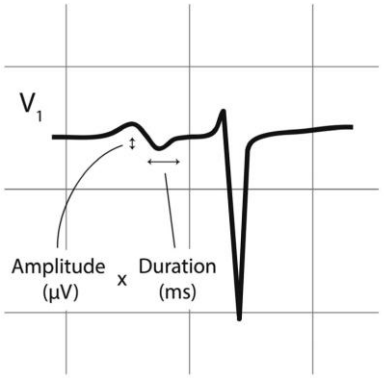




- **In elderly treated hypertensive patients (n=1191), LA enlargement is an independent predictor of ischemic stroke**

Pierdominco et al, American Journal of Hypertension 27(9), 201

P wave terminal forces and stroke



- 3129 community-dwelling adults aged ≥65 years
- Associations of ECG left atrial abnormality with brain infarcts
- Documented AF excluded
- Hypothesis: left atrial disease may produce a substrate for cardiac thrombus formation and embolization even in the absence of AF
- Increase in P-wave terminal force in lead V1 was associated with a higher baseline white matter grade
- associated with prevalent infarcts & non-lacunar infarcts

Table 1. Baseline Characteristics of Cardiovascular Health Study Participants, Stratified by Category of $PTFV_1$*

Characteristic†	$PTFV_1$=0 μV ms (n=758)	$PTFV_1$=207–2494 μV ms (n=799)	$PTFV_1$=2495–3780 μV ms (n=789)	$PTFV_1$=3781–19 474 μV ms (n=778)
$PTFV_1$, mean (SD), μV ms	0 (0)	1786 (471)	3088 (367)	5436 (1715)
Age, mean (SD), y	74.5 (5.2)	74.5 (4.9)	74.3 (4.8)	74.8 (5.2)
Men	300 (39.6)	318 (39.8)	337 (42.7)	308 (39.6)
Black	96 (12.7)	99 (12.4)	126 (16.0)	155 (19.9)
High school graduate	580 (76.5)	592 (74.1)	599 (75.9)	553 (71.1)
SBP, mean (SD), mm Hg	131.9 (19.6)	134.1 (19.80)	134.6 (20.5)	138.1 (22.3)
HDL, mean (SD), mg/dL	54.6 (14.6)	54.2 (14.5)	53.6 (14.5)	54.1 (14.5)
LDL, mean (SD), mg/dL	127.0 (33.7)	128.7 (32.7)	128.4 (33.9)	128.3 (35.2)
Coronary heart disease	119 (15.7)	126 (15.8)	133 (16.9)	188 (24.2)
Congestive heart failure	21 (2.8)	18 (2.3)	24 (3.0)	42 (5.4)
Diabetes status				
Normal	601 (80.2)	597 (75.9)	586 (75.0)	571 (74.1)
Impaired fasting glucose	67 (8.9)	88 (11.2)	85 (10.9)	89 (11.5)
Diabetes mellitus	81 (10.8)	102 (13.0)	110 (14.1)	111 (14.4)
Smoking status				
Never	344 (45.4)	412 (51.6)	360 (45.6)	373 (47.9)
Former	337 (44.5)	316 (39.5)	352 (44.6)	322 (41.4)
Current	77 (10.2)	71 (8.9)	77 (9.8)	83 (10.7)

ECG left atrial abnormality is associated with vascular brain injury in the absence of documented atrial fibrillation

Kamel H et al, Stroke. 2015;46:711-716

LA low voltage zones in AF

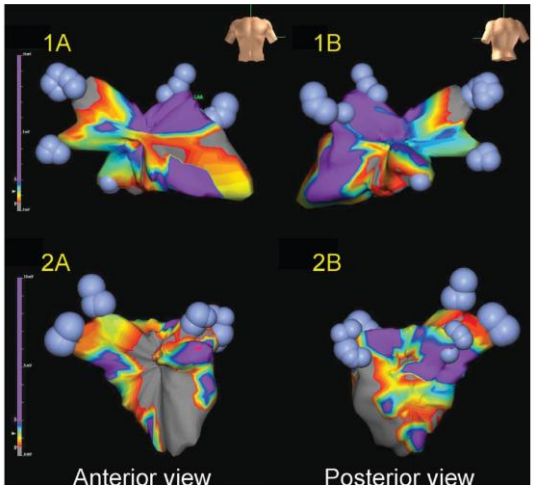
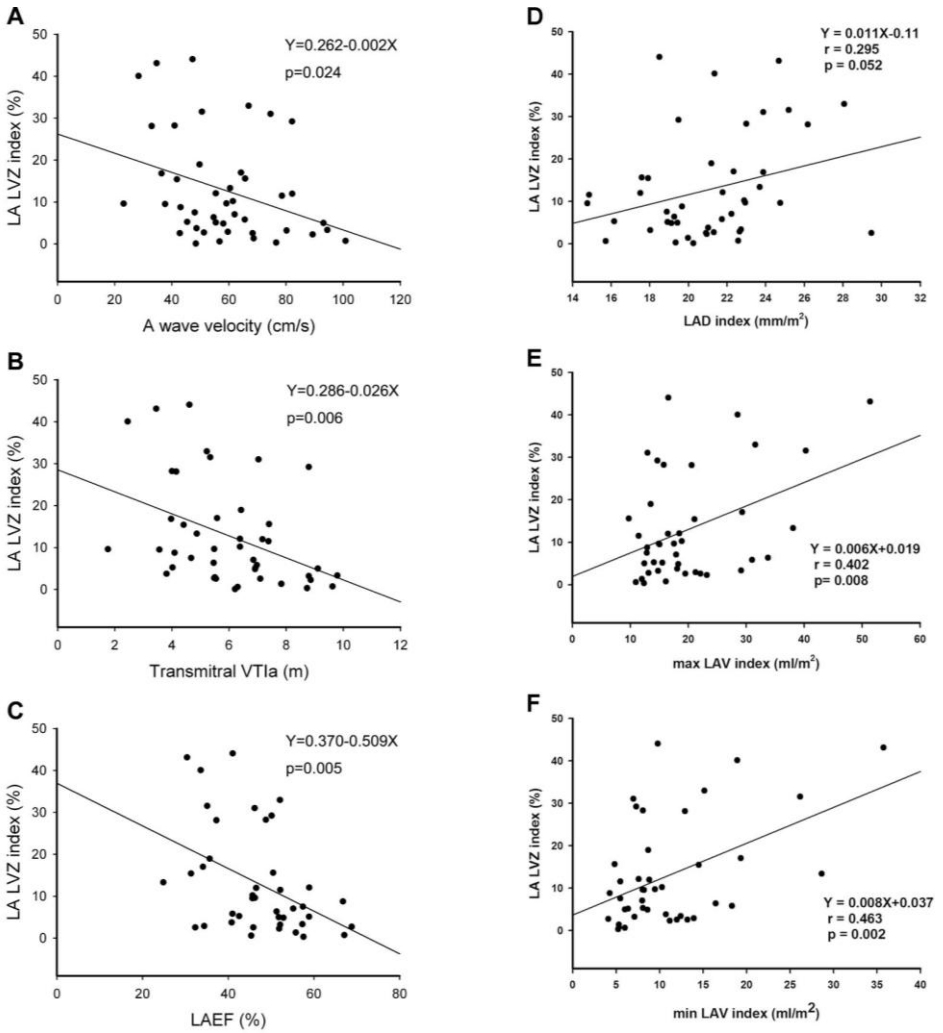


TABLE 1

Baseline Demographic, Echocardiographic, and Electrophysiologic Characteristics of Enrolled Patients

	Total 44 patients
Demographic Characteristics	
Age, year old	50.3 ± 10.7
Gender, M/F	33/11
Hypertension, n (%)	16 (36.4)
Persistent/paroxysmal AF, n (%)	3 (6.8)/ 41 (93.2)
Duration of symptomatic AF, years	4.92 ± 3.52
Number of anti-arrhythmic drugs	3 ± 1.12
Structural heart disease, n (%)	5 (11.4)



- **Study of association between atrial voltage properties and mechanical function of the LA**

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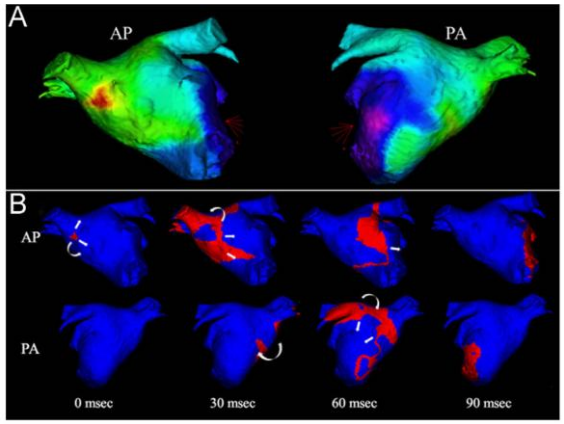
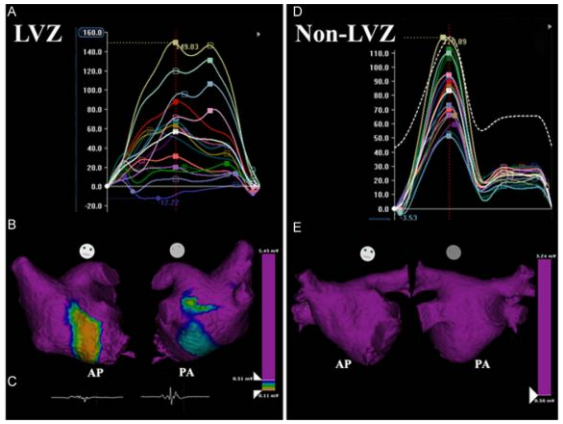
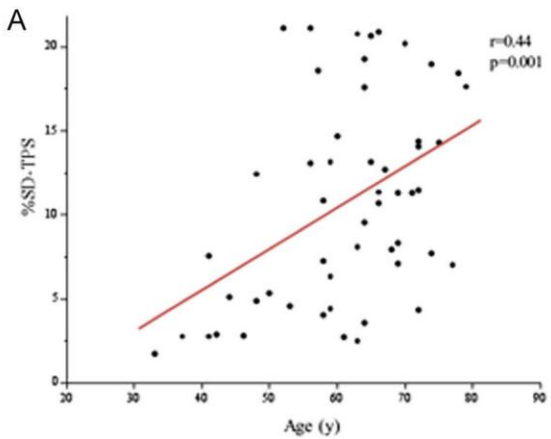
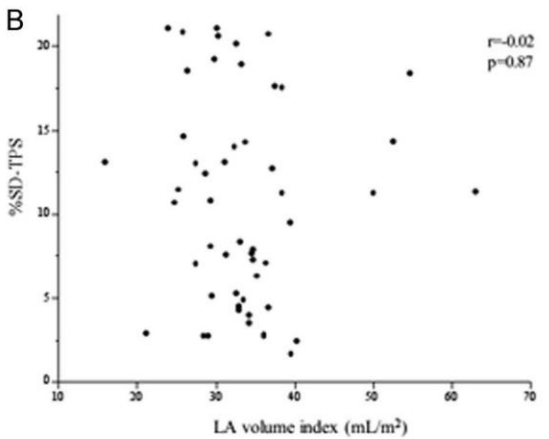
Sung et al. J Cardiovasc Electrophysiol. Vol. 19. pp. 165-171. 2008

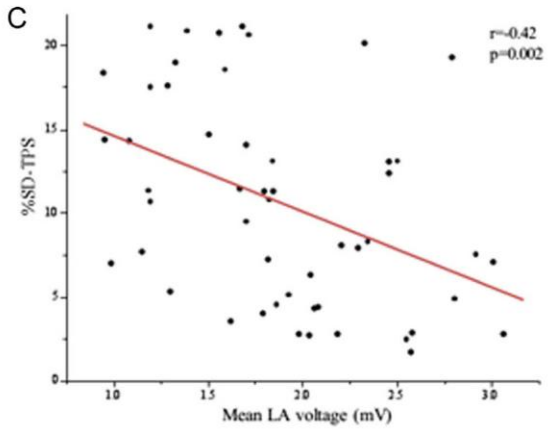
LA speckle tracking and EP substrate

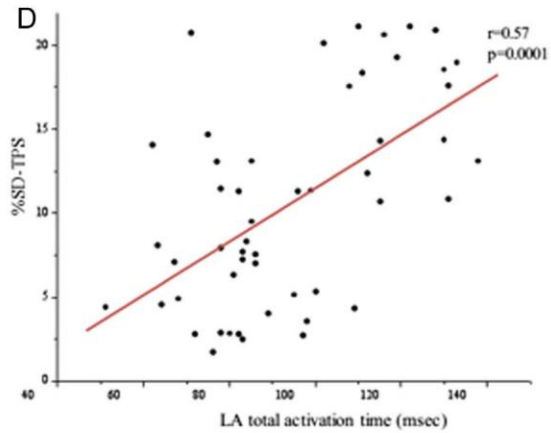








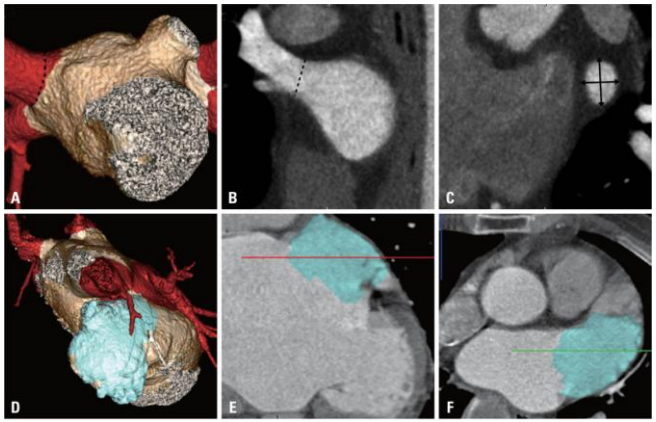




- 52patients with PAF undergoing PVI
- Standard deviation of the time to peak strain in each LA segment (%SD-TPS) was analyzed as an index of LA dyssyn- chrony using 3D-STE
- LA dyssynchrony and conduction delay greater in patients with low voltage zones

Watanabe Y et al. Heart Rhythm 2015;12:490–497

LA, LAA & PV dilatation and stroke



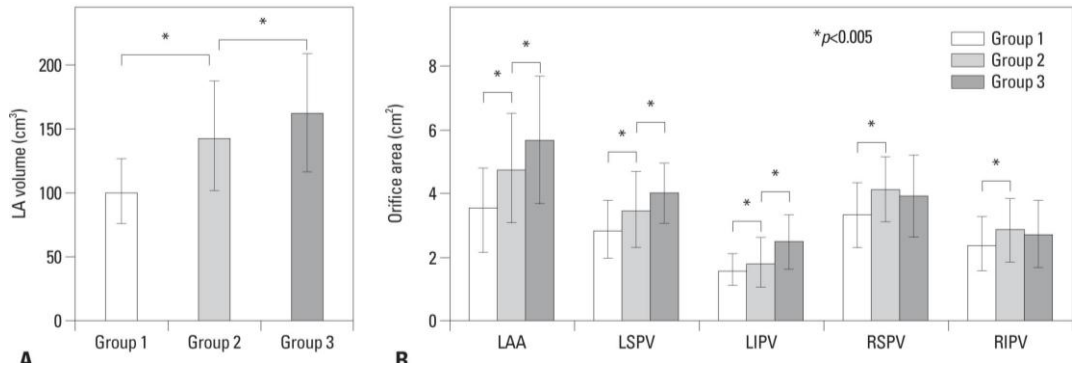
- Group I: 138 controls
- Group II: 138 AF patients
- Group III: 138 AF+ stroke

Table 1. Patient Demographic and Clinical Characteristics

	Control (n=138)	*p* value*	AF (n=138)	*p* value†	AF with stroke (n=138)
Age, yrs	66±9	1.0	65±8	0.87	66±8
Female, n	45 (33%)	0.514	40 (29%)	0.436	46 (33%)
Persistent AF, n	N/A		47 (34%)	<0.001	81 (59%)
Comorbidities, n					
CHF	4 (3%)	0.356	7 (5%)	0.791	8 (6%)
Hypertension	77 (56%)	1.0	77 (56%)	0.001	105 (76%)
Age >75 yrs	26 (19%)	0.04	14 (10%)	0.839	13 (9%)
Diabetes mellitus	31 (23%)	0.555	27 (20%)	0.119	38 (28%)
Dyslipidemia	39 (28%)	0.123	28 (20%)	0.882	29 (21%)
$CHADS_2$‡	1.35±0.95	1.0	1.36±1.05	0.006	1.72±0.88
$CHADS_2$	1.35±0.95	1.0	1.36±1.05	<0.001	3.72±0.88
CHA_2DS_2-VASc‡	1.86±1.15	1.0	1.75±1.24	0.014	2.14±1.08
CHA_2DS_2-VASc	1.86±1.15	1.0	1.75±1.24	<0.001	4.14±1.08
BMI	24.0±2.9	0.595	24.5±2.8	0.213	23.8±3.1
LVEF, %	68.1±5.5	0.003	63.3±7.8	1.0	62.8±11.0
Aspirin use, n	55 (40%)	<0.001	97 (70%)	0.517	92 (67%)

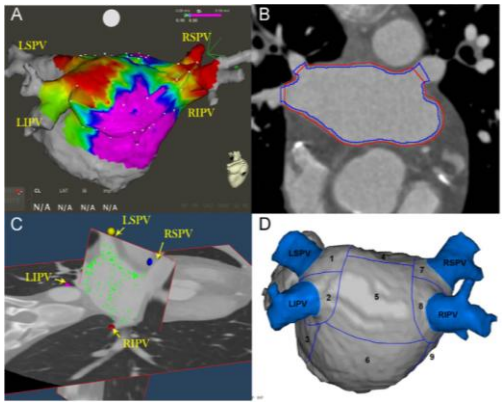
Stroke predictors

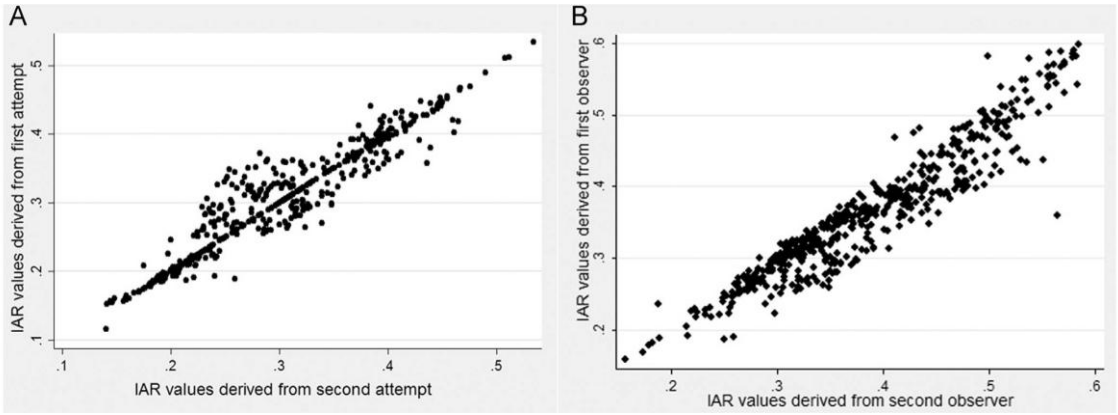
LA volume, per 10 cm^3	1.10 (1.03–1.17)	0.004	1.16 (1.09–1.23)	<0.001	1.09 (1.02–1.17)	0.014
LAA os area, cm^2	1.55 (1.36–1.76)	<0.001	1.53 (1.35–1.74)	<0.001	1.46 (1.26–1.69)	<0.001
LSPV os area, cm^2	1.25 (1.04–1.50)	0.015	1.55 (1.31–1.84)	<0.001	1.40 (1.15–1.69)	0.001
LIPV os area, cm^2	2.11 (1.52–2.92)	<0.001	2.66 (1.96–3.61)	<0.001	2.27 (1.64–3.15)	<0.001
RSPV os area, cm^2	0.86 (0.72–1.03)	0.106	1.10 (0.94–1.29)	0.214	1.05 (0.88–1.26)	0.575
RIPV os area, cm^2	0.90 (0.72–1.13)	0.363	1.11 (0.90–1.36)	0.320	0.95 (0.75–1.21)	0.681



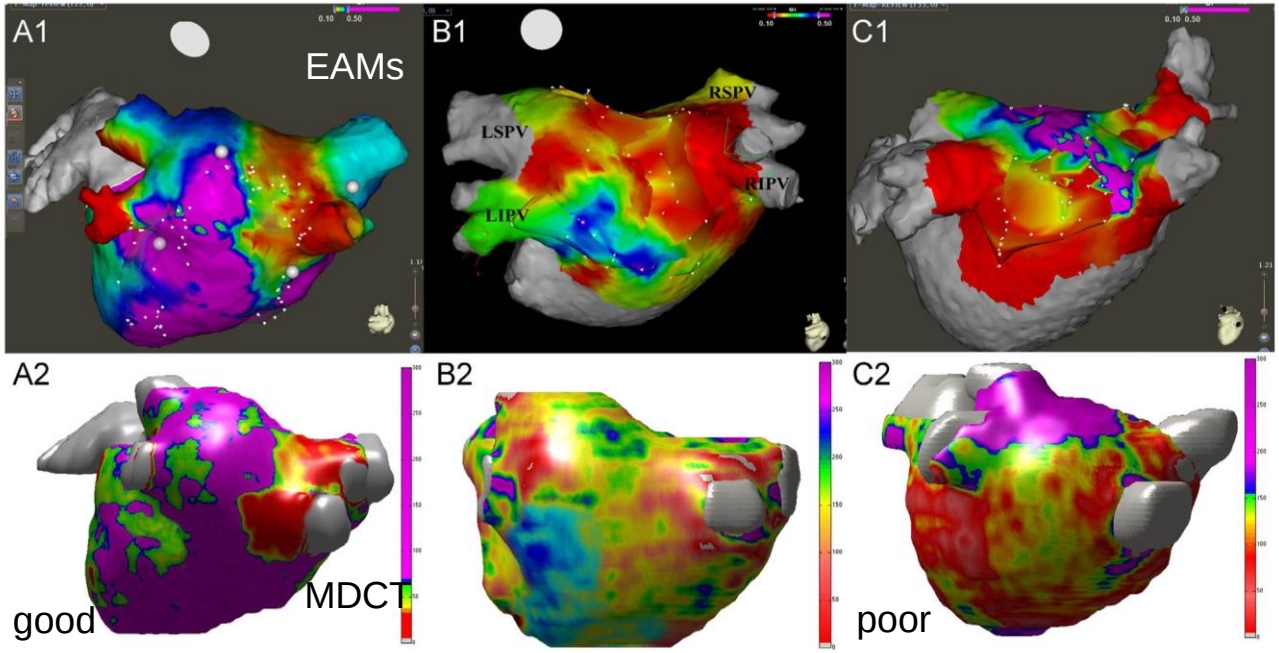
Lee JM etal, Yonsei Med J 55(6):1516-1525, 2014

MDCT correlation with LA low voltage zones





- Patients undergoing AF ablation
- Image attenuation ratio from contrast-enhanced multidetector computed tomography is associated with LA bipolar voltage
- Useful alternative to MR imaging



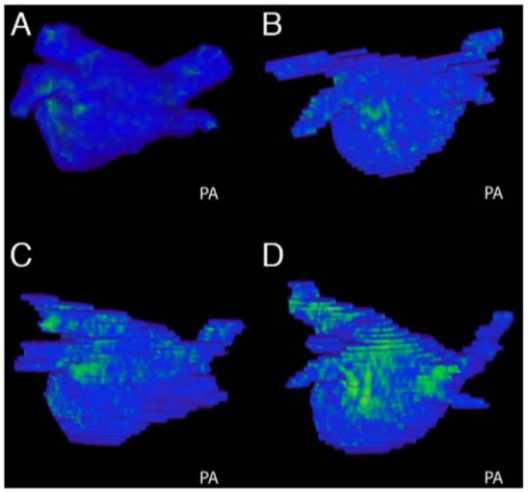
Ling Z et al. Heart Rhythm 2015

Atrial fibrosis by MR and stroke

The amount of DE-MRI–determined LA fibrosis could represent a marker for stroke

Table 1 Clinical Characteristics According to Stroke History

	Stroke (n = 36)	No Stroke (n = 351)	p Value
Age, yrs	64 ± 12	70 ± 7	<0.001
AF type			
Paroxysmal	15 (41.7%)	172 (49%)	NS
Persistent	21 (58.3%)	179 (51%)	NS
Warfarin use	25 (69.4%)	208 (59%)	NS
Female	23 (63.8%)	118 (33.6%)	<0.001
Diabetes mellitus	3 (8.3%)	47 (13.4%)	NS
Hypertension	24 (66.7%)	204 (58%)	NS
Congestive heart failure	2 (5.5%)	36 (10.2%)	NS
Age >75 yrs	8 (22.2%)	65 (18.5%)	NS
Risk score excluding strokes	1.02 ± 0.65	1 ± 0.9	NS
$CHADS_2$ score	3.02 ± 0.65	1 ± 0.9	<0.001
High risk: ≥2	36 (100%)	90 (25.6%)	NS
Moderate risk: 1	—	146 (41.6%)	—
Low risk: 0	—	115 (32.8%)	—



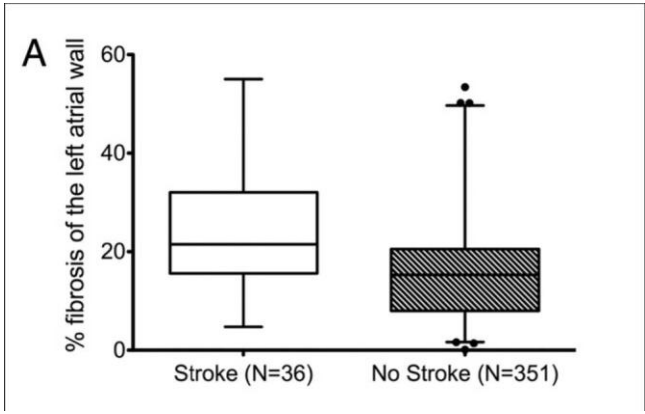


Figure 2 Relationship of LA Structural Remodeling and Stroke

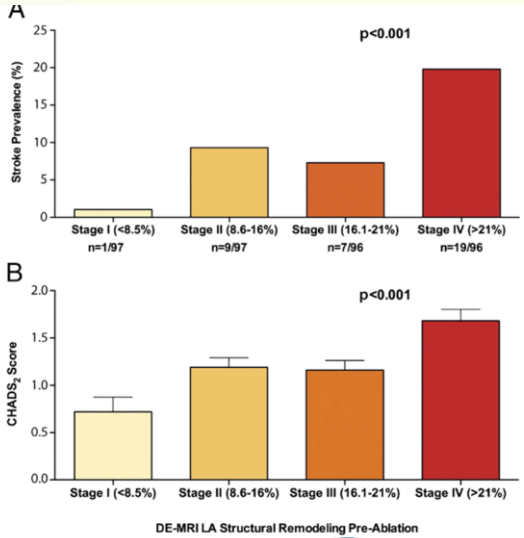
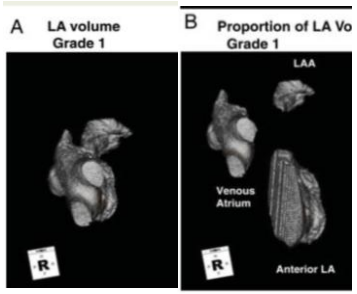


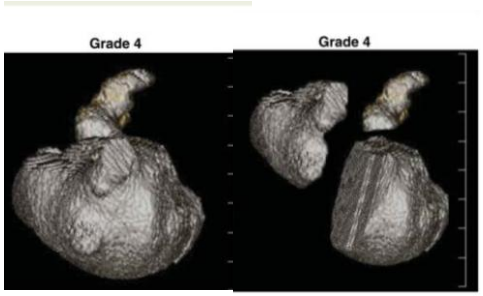
Table 4 Univariate and Multivariate Logistic Regression Analysis for Strokes

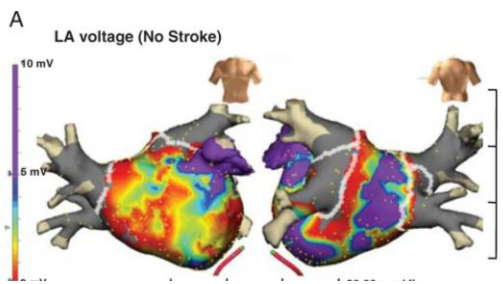
Univariate			Multivariate		
Variable	OR	p Value	Variable	OR	p Value
Persistent vs. paroxysmal AF	1.34	0.40	Persistent vs. paroxysmal AF	1.02	0.98
Warfarin use	0.64	0.22	Warfarin use	0.58	0.14
Female vs. male	3.49	<0.001	Female vs. male	3.11	0.003
Diabetes mellitus	0.58	0.38	Diabetes mellitus	0.43	0.21
Hypertension	1.44	0.32	Hypertension	1.35	0.51
Congestive heart failure	0.51	0.36	Congestive heart failure	0.36	0.19
Age >75 yrs	1.26	0.59	Age >75 yrs	1.18	0.58
LA remodeling stage	2.04	<0.001	LA remodeling stage	2.91	0.027
Stage II (Q2) vs. I (Q1)	9.8	0.018			
Stage III (Q3) vs. I	7.55	0.03			
Stage IV (Q4) vs. I	23.4	<0.001			

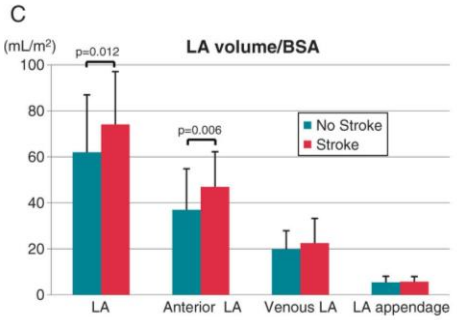
Daccarett et al, J Am Coll Cardiol 2011;57:831–8

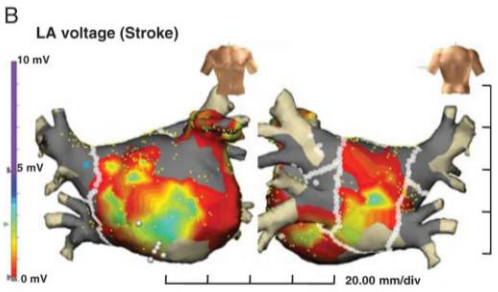
LA Voltages and prior stroke in AF











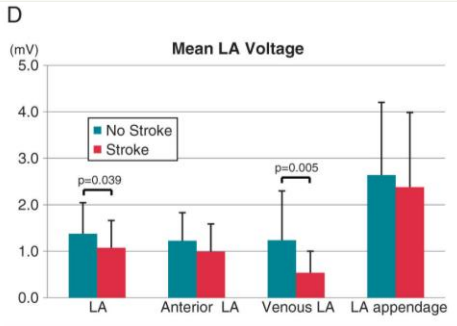


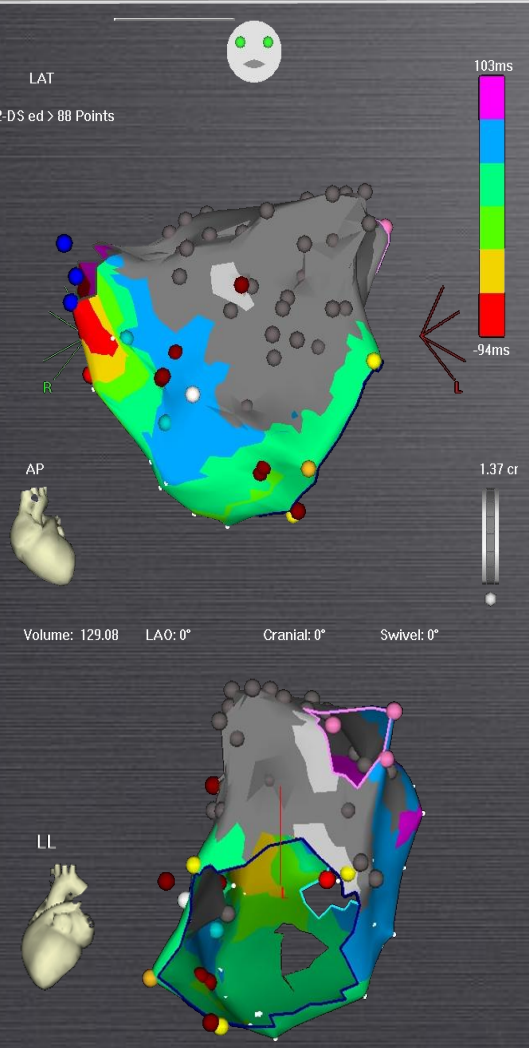
Table 4 Degree of left atrial remodelling in patients with and without stroke

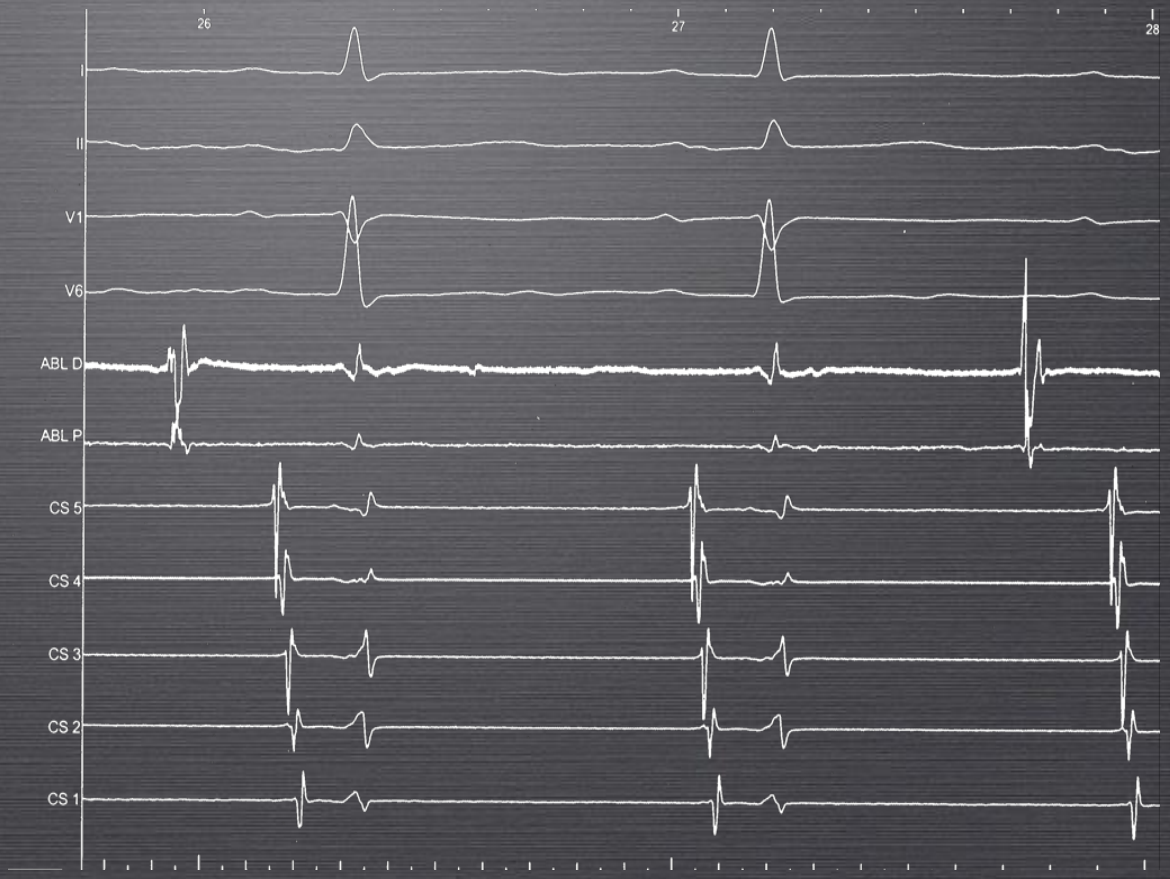
	No stroke (n = 326)	Stroke (n = 22)	P value
LA volumes/BSA (mL/m^2)			
Entire LA volume	61.5 ± 25.5	74.1 ± 23.0	$P = 0.012$
Anterior LA volume	36.9 ± 17.8	46.9 ± 15.3	$P = 0.006$
Venous LA volume	19.8 ± 8.0	22.5 ± 10.8	$P = 0.074$
LAA volume	5.4 ± 2.6	5.7 ± 2.3	$P = 0.329$
Relative volumes of regional LA (%)			
Anterior LA volume	59.3 ± 7.6	62.2 ± 8.0	$P = 0.044$
Venous LA volume	32.1 ± 7.4	30.6 ± 7.6	$P = 0.185$
LAA volume	8.6 ± 3.3	7.2 ± 2.1	$P = 0.025$
LA voltage (mV)			
Mean LA voltage	1.4 ± 0.7	1.1 ± 0.6	$P = 0.039$
Anterior LA	1.2 ± 0.6	1.0 ± 0.6	$P = 0.068$
Venous LA	1.2 ± 1.1	0.5 ± 0.5	$P = 0.005$
LAA	2.6 ± 1.6	2.4 ± 1.6	$P = 0.259$
LV function			
LVEF (%)	59.6 ± 8.6	63.0 ± 8.1	$P = 0.041$
E/E'	9.4 ± 3.8	10.5 ± 3.2	$P = 0.120$
Hypertension	144 (44.2%)	12 (54.5%)	$P = 0.216$
Renal insufficiency	6 (1.8%)	0 (0.0%)	$P = 0.673$
Recurrence	62 (19.0%)	0 (0.0%)	$P = 0.041$

Electroanatomical remodelling of LA, estimated by LA volume and endocardial voltage, has significant relationship with the risk scores or events of stroke in patients with non-valvular AF.

Park JH et al, Europace (2011) 13, 1541–1549

LAA dissociation

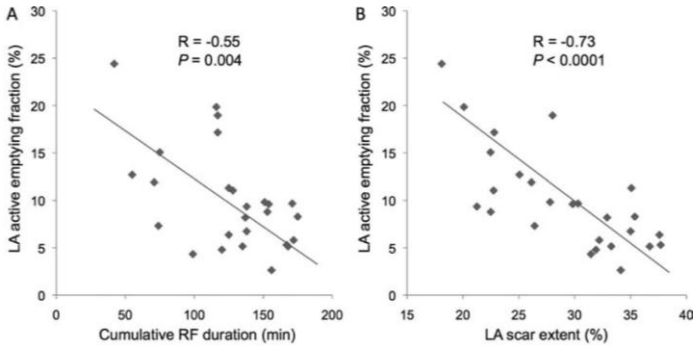




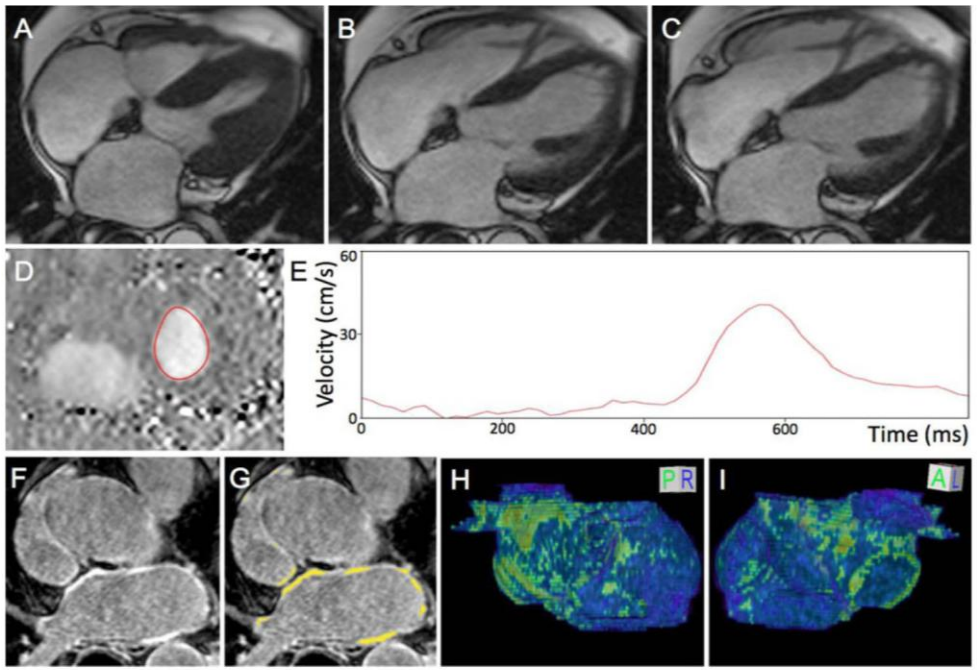
Effect of ablation on LA function

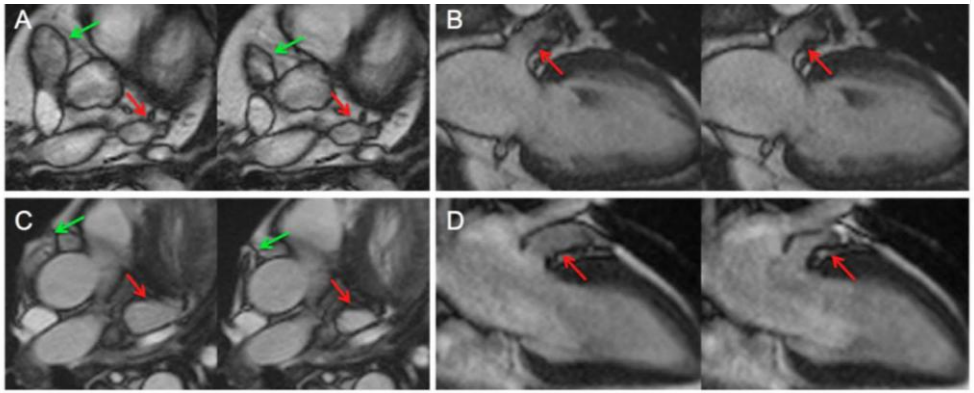
LA contractility and compliance are markedly impaired &. LA dysfunction is closely related to scar burden

Baseline Characteristics	
Clinical Characteristics	
Age (years)	54 ± 8 (40–67)
Gender (M:F)	25:1
$CHADS_2DS_2$-VASc score	1.1 ± 0.9 (0–3)
NYHA	1.1 ± 0.3 (1–2)
Dyspnea at exertion	3/26
Structural heart disease	11/26
ICM	4/26
NICM	7/26
AF duration (months)	77 ± 60 (12–220)
PsAF duration (months)	12 ± 9 (2–39)
History of amiodarone use	11/26
Anticoagulant therapy	26/26
Procedural characteristics	
Baseline LAA CL (ms)	148 ± 20 (124–201)
AF termination at 1st procedure	24/26
Recurrence after 1st procedure	22/26
Total no of procedures	2.2 ± 0.7 (1–4)
Ablation sites	
PVI	26/26
Cavotricuspid isthmus	26/26
Left isthmus	22/26
Roof	21/26
CFAE	25/26
RA	12/26
Cumulative RF duration (min)	126 ± 37 (42–175)



max precontraction min





www.escardio.org/EHRA

Cochet H et al, J Cardiovasc Electrophysiol, Vol. 25, pp. 671-679, July

Summary

- The standard risk factors account for the major part of stroke risk in atrial fibrillation
- There is likely a significant local left atrial component contributing to stroke risk in patients with atrial fibrillation
- Left atrial dysfunction or remodelling may contribute to stroke risk even without documented AF
- LA electrophysiological parameters may provide an early indication of this remodelling